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Seizure logging: A new approach to synchronized cable-free EEG and video recordings of seizure activity in mice

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ABSTRACT

We describe a new cable-free, non-telemetric method for synchronized electrophysiological and video recordings of seizure activity in freely moving mice. The electrophysiological recordings were made by a head-mounted 4-channel data-logging device, allowing the mouse to move freely in its cage, and even to be moved from cage to cage under ongoing recording. Seizures were studied in Synapsin I/II double knock-out (SynDKO) mice, a genetically engineered mouse line that shows seizures upon daily handling procedures such as tail lifting during cage changes, much in resemblance to the more studied El mouse. The ability to elicit seizures through daily handling in SynDKO mice undergoing electrophysiological recording is a significant improvement in comparison to the traditional cable-based set-up. Furthermore, with its four channels and a sample rate of up to 500 Hz, the data-logging device opens for more varied electrophysiological studies than other available cable-free systems.

1. Introduction

Rodent seizure and epilepsy models are valuable tools in the study of generation and spread of seizure activity. Central to the use of all such models is the ability to monitor ongoing pathological electrophysiological activity, most often in the form of electroencephalograms (EEG). Furthermore, relating the electrophysiological findings to detailed behavioral analysis may give additional insight into the structures underlying the epileptic phenomena (Moraes et al., 2005). With the development of modern genetic engineering, the number of potential rodent seizure and epilepsy models has rapidly increased, particularly in the mouse where currently mutations in 103 different genes are known to cause epileptic phenomena (Frankel, 2009). The small size of the mouse is however a challenge for electrophysiologists. Yet, successful electrophysiological recordings have been made during seizures in freely behaving animals by signal transmission through cables and the use of swivel-devices. Such cable-based systems hardly impose problems for studies of seizures that rely on electrical or chemical induction. However, in many epilepsy models, the most studied being the El mouse, seizures appear during complex stimulus situations such as daily handling procedures (Etholm and Heggelund, 2009; Kitami et al., 2004; Todorova et al., 1999). In such studies cable-based systems cause problems because one would try to mimic situations where seizures are normally seen. For instance, the swift movement of the animal from one cage to another that is typical during regular cage changes, may be hindered by the cord of the cable-based system, also when the animal is allowed to move freely within the cage by the use of a swivel. Even such small perturbations can reduce or abolish seizures altogether in certain models (Etholm and Heggelund, 2009). This is particularly relevant with new seizure models where the specific factors constituting the stimulus situation are less clearly defined.

Problems with evoking seizures during EEG-recording can be bypassed by using pharmacological agents (Nakano et al., 1994), but this may seriously change the nature of the seizure studied. The risk of changing the phenomenon studied is also present in cases where the stimulus intensity is increased by for instance replacing simple cage changing procedures with more traditional tossing procedures (Imaizumi et al., 1959), or where one is changing such tossing regimes to make them practical with cable-tethered animals (Etholm and Heggelund, 2009; Kitami et al., 2004; Suzuki and Nakamoto, 1977). Moreover, such elaborate movement regimes (Imaizumi et al., 1959) can induce large movement artifacts, especially during the initial parts of the seizures that are often of great interest. Although elegant custom-made electronic designs have been successfully applied to remove artifacts due to passive movement of the animal (Ishida et al., 1993), such designs are not widely used, possibly due to the complexity of the set-up and the stimulus situation. In general, one should try to keep the seizure induction as

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gentle as possible both with regards to animal welfare and quality of the scientific results.

Recently, elegant telemetric devices have been developed for electrophysiological recordings without cables that may be useful in mouse epilepsy models relying on daily handling for seizure elicitation. The devices have been developed to decrease the restraint of the animal during recordings, and increase the flexibility of the recording situation (Weiergräber et al., 2005). However, such systems have so far showed considerable limitations both due to their low number of recording channels and low sampling rate.

In this study, we present a new system for combined cable-free, non-telemetric EEG-recordings and synchronized video recordings of seizure behavior in freely moving mice. We have tested the system on Synapsin I/II- double knock-out mice (SynDKO mice), which show seizures in connection with daily handling procedures such as tail lifting during cage changing (Etholm and Heggelund, 2009). During cable-based EEG-recordings in SynDKO mice, seizures evoked by tail lifting are abolished (Etholm and Heggelund, 2009). Seizures can however still be evoked by modifications of the tossing procedure described by Imaizumi et al. (1959). Through the use of a 4-channel head-mounted data-logging unit, EEG activity during seizures could be recorded at different cortical sites after simple tail lifting from one cage to another, indicating a lowered impact of the recording equipment on the animal, and a higher flexibility of the recording situation compared to cable-based systems. Moreover, the EEG activity could be synchronized with video-recorded animal behavior by means of an infrared signaling input to the logger, and this provided possibilities for detailed comparison of brain activity and specific behavioral elements during seizures. The versatility of this system is further increased by a high sampling rate of up to 500 Hz, allowing recordings of more varied signals than those found in the classical EEG-range.

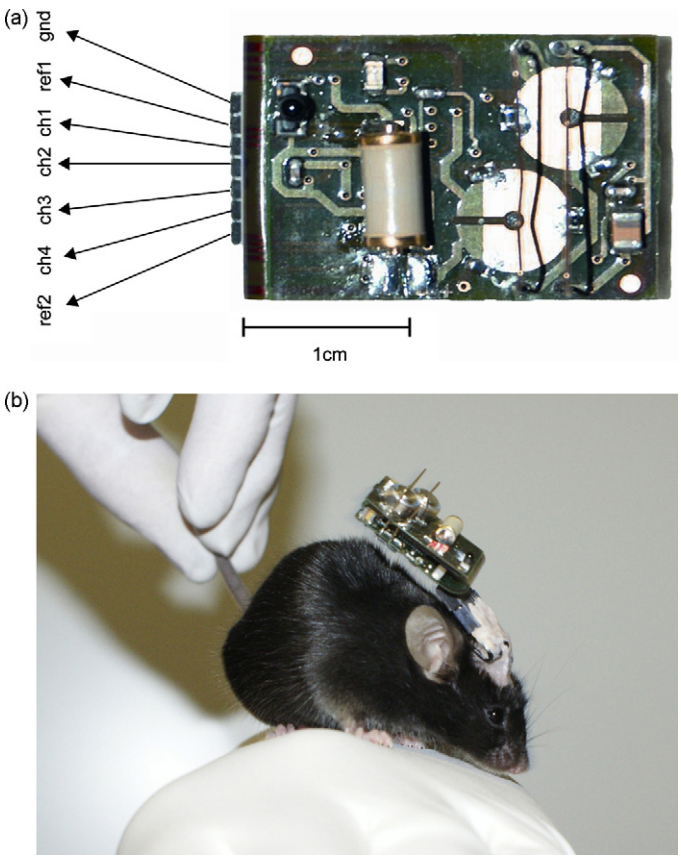

Fig. 1. (A) Data-logging device. (B) Mouse with mounted device.

2. Materials and methods

2.1. Data-logging device

The device called NeuroLogger® (NewBehavior AG, Zürich, Switzerland) has a weight of 2.8 g including batteries and can be plugged into or removed from a connector embedded in a dental cement socket on the skull of the animal (Fig. 1). We used a commercially available version of a prototype system described by Vyssotski et al. (2009) for use on pigeons. Briefly, it contains 4 input channels for electric signals, 2 reference channels, 1 channel for a movement sensor, and 1 channel for an infrared receiver. Preamplification, analog-to-digital (AD) conversion (unity gain buffer, AC input range ±750 μV, 500× gain, band-pass filter 1–70 Hz, ADC resolution 8 bits), and data storage capacity up to 512 MB, are handled by a microprocessor. Reference channels can be internally connected within the data-logging device when independent references are not required. In this case, 6 connecting pins are used (4 input channels, 1 reference channel, 1 ground). This configuration was used in the current study. Sampling rates can be selected by the user in the range between 64 and 500 Hz. Battery (1.4 V standard hearing aid Zink-Air batteries) runtime varies with sampling frequency and quality of supplier from 36 to 72 h. Data can be downloaded offline from the microprocessor to a computer in hexadecimal format through an USB interface cable. For basic design and circuitry of the NeuroLogger, see Vyssotski et al. (2009). The version described here was industrialized under license from the University of Zürich and differs from the initial prototype chiefly in five points: (i) upper sampling rate is set to 500 Hz to handle a wide EEG-signal range yet allowing recordings over several days, (ii) the logger contains a movement sensor obviating the need for recording electromyograms to document movements, (iii) it is equipped with battery holders for hearing aid batteries in order to avoid soldering of leads to batteries, (iv) electrodes are pre-soldered to pins connecting to the data logger to avoid soldering during implantation, and (v) it contains additional circuitry for an infrared receiver permitting wireless event registration.

2.2. Surgical procedure

Experimental procedures were approved by the Norwegian Animal Research Authority according to the Norwegian Animal Welfare Act and the European Communities Council Directive of 24 November 1986 (86/609/EEC).

Synapsin knock-out mice were developed by homologous recombination as previously described (Chin et al., 1995; Ferreira et al., 1998). Synapsin double knock-out mice and their wild type strain were derived from a combined C57BL/6 129/Sv background, whereas the Synapsin I single knock-out mice were bred on a C57BL/6 background with regular back-crossings. Animals aged 2–6 months were used in this study. Electrode implantations were done stereotaxically under general anesthesia using a mixture of 25% Hypnorm (0.315 mg/ml fentanyl and 10 mg/ml fluanisone; Janssen-Cilag, High Wycombe, UK); 25% Dormicum (5 mg/ml midazolam; Roche, Basel, Switzerland) and 50% H_2O, at a dosage of 0.07–0.1 ml/10 g s.c. Stainless steel or gold screws were used as EEG-electrodes. They were placed above both left and right frontal and parietal cortices, at coordinates with reference to bregma and midline respectively (Paxinos and Franklin, 2004): at frontal cortices, 1.5–2.3 mm anterior, 1.3–2.0 mm lateral, and at parietal cortices, 3.5–4.5 mm posterior, 1.5–2.5 mm lateral. The variations in electrode positioning were made to avoid larger cerebral vessels. As reference electrode we used either a stainless